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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,154	12/26/2001	Toshiaki Tagawa	P21462	2932

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EXAMINER
COUNTS, GARY W

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/926,154	Applicant(s) TAGAWA ET AL.	
	Examiner Gary W. Counts	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the claims

The amendment filed on June 16, 2003 is acknowledged and has been entered.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

2. Claims 1, 4-6, 8-15, 19, 21-23, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Allen et al (US 5,527,528).

Allen et al disclose liposomes (microparticle) containing an anti-tumor compound in liposome entrapped form. Allen et al disclose monoclonal antibodies coupled to the liposome by polyethylene glycol chains (col 2). Allen et al disclose that these antibodies are specific for tumor-associated antigens and provides for localizing the liposome at the tumor site (non-free target). Allen et al disclose that that the antibody may be attached to the liposome by covalent or noncovalent attachment methods (col 9, lines 29-30).

With respect to the free target as recited in the instant claims. Allen et al disclose the use of a monoclonal antibody which is specific for a particular tumor epitope and therefore the antibody would have an affinity for the non-free target even in the presence of free targets.

3. Claims 1, 4, 9, 13, 16, and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Buechler et al. (US 6,156,521).

Buechler et al disclose an antibody conjugate comprising an antibody (ligand) coupled to a signal generating element (col 3, lines 20-22). Buechler et al disclose that this signal generating element can be particles (col 8, lines 20-28). Buechler et al disclose that the antibody specifically binds to specific regions of a form of troponin (analyte) or a group of analyte forms (col 3). Buechler et al further disclose that the antibody can be a sensitive antibody which binds specifically to a target such that it will exhibit a preferential detection of one form or group of forms of troponin in an immunoassay, and it will have a greater affinity for something it specifically binds than for something it does not specifically bind (col 7). Buechler et al disclose that the antibody (ligand) will preferentially recognize a ternary complex of troponin (non-free target) in the presence of both free troponin I and T (free target) (col 18). Buechler et al disclose that the antibodies can be conjugated to the signal generators in a variety of ways using heterobifunctional reagents.

With respect to the dissociation constant between the target and one ligand as recited in the instant claims. Buechler et al disclose the ligand-bonded complex as

claimed and therefore, it would inherently comprise the dissociation constant between the target and one ligand as recited in the instant claims.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 2, 7, 20 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allen et al in view of Tagawa et al.

See above for teachings of Allen et al.

Allen
~~Tagawa~~ et al differ from the instant invention in failing to specifically teach that the water-soluble macromolecule is polyalkylene glycol.

Tagawa et al disclose the use of polyalkylene glycol with liposomes (col 2, lines 1-18). Tagawa et al disclose that the use of this polyalkylene glycol provides for a drug-containing antibody-bonded liposome having the nature of being captured in the reticuloendothelial system improved.

It would have been obvious to one of ordinary skill in the art to incorporate polyalkylene glycol as taught by Tagawa et al with the liposome of Allen et al because Tagawa et al shows that the use of this polyalkylene glycol provides for a drug-containing antibody-bonded liposome having the nature of being captured in the reticuloendothelial system improved.

With respect to the number of ligands bonded to the microparticle as recited in the instant claims, the optimum number of ligands can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art. Further, it has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454,456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation ." Id. At 458,105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272,276, 205 USPQ 215, 218-219 (C.C.P.A. 1980).

6. Claims 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buechler et al in view of Nichtl et al (US 5,972,720).

See above for teachings of Buechler et al.

Buechler et al differ from the instant invention in failing to teach a water-soluble marcromolecule is bonded to the microparticle.

Nichtl et al disclose particles to the surface of which biomolecules are absorbed, wherein the composition additionally contains polyethylene glycol. Nichtl et al disclose that this composition can be used as a detection reagent in immunological test methods such as for troponin. Nichtl et al disclose that polyethylene glycols substituted by thiol are excellently suitable for the stabilization of biomolecule particle conjugates and as a results of the stronger binding of the substituted polyethylene glycols to the particle

surface compared to stabilizers of the state of the art a substantial improvement is achieved with regard to the stability of the conjugates thus leading to an improved long-term stability and a lower aggregation tendency in solution to a better stability towards changes in the environmental conditions and an improved test function (col 2).

It would have been obvious to one of ordinary skill in the art to incorporate polyethylene glycol as taught by Nichtl et al into the ligand complex of Buechler et al because Nichtl et al discloses that polyethylene glycols substituted by thiol are excellently suitable for the stabilization of biomolecule particle conjugates and as a results of the stronger binding of the substituted polyethylene glycols to the particle surface compared to stabilizers of the state of the art a substantial improvement is achieved with regard to the stability of the conjugates thus leading to an improved long-term stability and a lower aggregation tendency in solution to a better stability towards changes in the environmental conditions and an improved test function.

7. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Allen et al in view of Lindhofer et al (US 6,294,167).

See above for teachings of Allen et al.

Allen et al differ from the instant invention in failing to teach the ligand-bonded complex in a pharmaceutical composition.

Lindhofer et al disclose immunoliposomes which have monoclonal antibodies bound on their surfaces. Lindhofer et al disclose that these immunoliposomes are contained in pharmaceutical compositions (col 6). Lindhofer et al disclose that these compositions provide for particular tumor cells, to be distinguished from other cells on account of the recognition of

specific marker antigens and are therefore suitable for immunological cell therapy and the pharmaceutical compositions lend themselves to in vivo and in vitro therapy of different tumor types (col 1).

It would have been obvious to one of ordinary skill in the art to incorporate pharmaceutical compositions as taught by Lindhofer et al with the liposomes of Allen et al because Lindhofer et al shows that these compositions provide for particular tumor cells, to be distinguished from other cells on account of the recognition of specific marker antigens and are therefore suitable for immunological cell therapy and the pharmaceutical compositions lend themselves to in vivo and in vitro therapy of different tumor types.

Response to Arguments

Applicant's arguments filed June 16, 2003 have been fully considered but they are not persuasive.

Applicant argues that Allen does not teach or suggest a ligand-bonded complex comprising a microparticle directly or indirectly bonded to at least one ligand, the ligand having an affinity for a target substance, wherein the affinity allows specific binding of the complex to a non-free target in the presence of both a non-free target and a free target. This is not found persuasive because the monoclonal antibody disclosed in Allan et al is specific for an antigen on highly proliferating cells in lung squamous carcinoma (non-free target) (col 2, lines 53-56, column 8, lines 6-10) and in view of the highly specific binding of the monoclonal antibody, it would only bind to the non-free target and should there be any free target present it would only bind to the non-free target. Therefore, the monoclonal antibody of Allen et al provides the function of

binding to the non-free target in the presence of both a non-free target and a free target. Applicant further states that their invention contains plural numbers of the ligand bonded to the surface of the microparticle, thereby increasing its affinity. In response to applicant's statement, it is noted that the features upon which applicant relies (plural numbers of the ligand bonded to the surface of the microparticle thereby increasing its affinity) are not recited in the instantly rejected claims. Applicant's further direct Examiner's attention at column 2, lines 43-48 and column 12, line 38 et seq. Applicant argues that Allen specifically discloses prior to liposome administration, administration of multivalent species to accelerate clearance of nonspecifically-bound antibodies from the bloodstream. This argument is not found persuasive because applicant is arguing an embodiment that is not relevant to the disclosed embodiment. Examiner has not relied upon the embodiment in which applicant is arguing. Examiner has relied upon the embodiment in which antibody molecules are coupled to the liposome surface by polyethylene glycol chains containing at their free ends a functionalized reactive group to which the antibody molecules are covalently attached (col 2, lines 20-24). Applicant's argument is directed to an embodiment in which antibody molecules are injected into a subject effective to bind specifically to tumor-associated antigen and having attached ligand molecules (such as biotinylated antibodies) and after 24-48 hour period of time, liposomes (comprising avidin) are administered to the subject, by parenteral injection (see col 2, lines 25-31 and column 12 lines 17-47). For the reasons stated above, it is the Examiner's position that Allen et al still reads on the instantly recited claims.

Applicant argues that Buechler does not teach or suggest a ligand-bonded complex comprising a microparticle directly or indirectly bonded to at least one ligand, the ligand having an affinity for a target substance, wherein the affinity allows specific binding of the complex to a non-free target in the presence of both a non-free target and a free target. Applicant states that their invention contains plural numbers of the ligand bonded to the surface of the microparticle, thereby increasing its affinity. In response to applicant's statement, it is noted that the features upon which applicant relies (plural numbers of the ligand bonded to the surface of the microparticle thereby increasing its affinity) are not recited in the instantly rejected claims. Applicant further argues that in contrast to Applicant's invention, in the embodiment utilized by the rejection in an attempt to establish inherency merely refers to the use of different antibodies to bind to different components. It is true that this can be done by the embodiment Applicant refers to (col 18, line 56 et seq.). However, this is not the embodiment Examiner relies upon. Examiner directs Applicants attention to column 18 lines 6-55, in which Buechler et al discloses antibodies coupled to a signal generator (microparticle). Buechler et al discloses that these antibodies bind to the troponin complexes or to the uncomplexed troponin T and I (free target). Accordingly, Buechler et al still reads on the instantly recited claims.

Applicant argues that Buechler relates to a test of a blood sample suspected to contain troponin and that there is no disclosure of distinguishing cell-bound target from a free-floating target. In response to the applicant's argument that the disclosure fails to show certain features of the applicant's invention, it is noted that the features upon

which applicant relies (i.e. distinguishing cell-bound target from a free-floating target) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns,* 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore, it is the Examiner's position that the Buechler et al reference still reads on the binding profile of the recited claims.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (703) 305-1444. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gary W. Counts
Examiner
Art Unit 1641
August 21, 2003

LONG V. LE
SUPERVISORY PATENT EXAMINER
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08/22/03